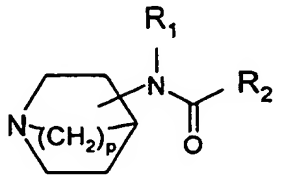
CLAIMS

1. A compound which is a quinuclidine amide derivative of formula (I):



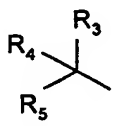
(I)

wherein

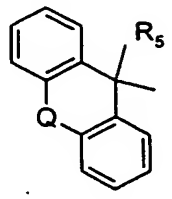
R_1 represents a hydrogen atom or an straight or branched, optionally substituted lower alkyl group;

R_2 represents a group of formula i) or ii)

i)



ii)



wherein

R_3 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

R_4 represents a group selected from optionally substituted lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkynyl, cycloalkyl, cycloalkylmethyl, phenyl, benzyl, phenethyl, 2-furyl, 3-furyl, 2-thienyl or 3-thienyl;

and R_5 represents a hydrogen atom or a hydroxy, methyl, or $-CH_2OH$ group;

the benzene rings in formula ii) and the cyclic groups represented by R_3 and R_4 being each independently optionally substituted by one, two or three substituents selected from

halogen, straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, nitro, cyano, $-CO_2R'$ or – NR'R", wherein R' and R" each independently represents a hydrogen atom or a straight or branched, optionally substituted lower alkyl group or R' and R" together with the atom to which they are attached form a cyclic group;

Q represents a single bond or a $-CH_2-$, $-CH_2-CH_2-$, -O-, $-O-CH_2-$, -S-, $-S-CH_2-$ or -CH=CH- group;

p is 1 or 2 and the amide group is at positions 2, 3 or 4 of the azabicyclic ring;

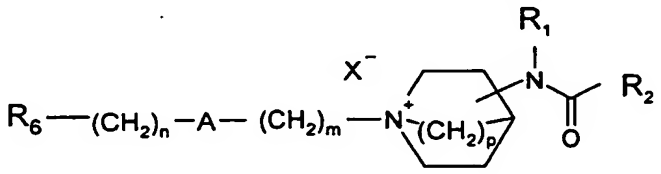
or pharmaceutically acceptable salts thereof, including quaternary ammonium salts;

and all individual stereoisomers and mixtures thereof;

with the proviso that when p is 2, the amide moiety is in position 3 of the quinuclidine ring, R_1 is hydrogen and R_3 and R_4 are both unsubstituted phenyl, then

-when said compound is not a pharmaceutically acceptable salt or is a HCl salt, then R_5 cannot be one of hydrogen or hydroxy; and
- when said compound is a quaternary ammonium salt having a methyl group attached to the nitrogen atom of the quinuclidine ring, then R_5 cannot be hydroxy.

2. A compound according to claim 1 which is a quaternary ammonium salt of formula (II)



(II)

wherein R_1, R_2 and p are as defined in claim 1;

m is an integer from 0 to 8;

n is an integer from 0 to 4:

A represents a group selected from $-CH_2-$, -CH=CR'-, -CR'=CH-, -CR'R''-, -C(O)-, -O-, -S-, $-S(O)-$, $-S(O)_2-$ and –NR'-, wherein R' and R'' are as defined in claim 1;

R_6 represents a hydrogen atom, or a group selected from straight or branched, optionally substituted lower alkyl, hydroxy, straight or branched, optionally substituted lower alkoxy, cyano, nitro, -CH=CR'R'', -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R'', -NR'C(O)OR'', -NR'C(O)NR'', cycloalkyl, phenyl, naphthanelyl, 5,6,7,8-tetrahydronaphthanelyl, benzo[1,3]dioxolyl, heteroaryl or heterocyclyl; R' and R'' being as defined in claim 1; and wherein the cyclic groups represented by R_6 are optionally substituted by one, two or three substituents selected from halogen, hydroxy, straight or branched, optionally substituted lower alkyl, phenyl, -OR', -SR', -NR'R'', -NHCOR', -CONR'R'', -CN, $-NO_2$ and -COOR'; R' and R'' being as defined in claim 1; and

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid.

and all individual stereoisomers and mixtures thereof;

with the proviso that when p is 2, the amide moiety is in position 3 of the quinuclidine ring, R_1 is hydrogen, R_3 and R_4 are both unsubstituted phenyl and R_5 is hydroxy, then in the compounds of formula (II) the sequence $R_6 - (CH_2)_n - A - (CH_2)_m -$ cannot be a methyl group.

3. A compound according to claim 1 or claim 2 wherein R_1 is hydrogen, methyl or ethyl.

4. A compound according to claim 3, wherein R_1 is hydrogen.

5. A compound according to any one of the preceding claims, wherein R_2 is a group of formula i), wherein R_3 is a group, which is optionally substituted with one or more halogen atom(s), selected from phenyl, 2-thienyl, 3-thienyl or 2-furyl

6. A compound according to claim 5, wherein R_2 is a group of formula i), wherein R_3 represents a group phenyl, 2-thienyl or 2-furyl which are optionally substituted with one or more halogen atom(s).

7. A compound according to any one of claims 5 and 6, wherein R_2 is a group of formula i), wherein R_3 represents phenyl or 2-thienyl.

8. A compound according to any one of the preceding claims, wherein R_4 represents a linear group selected from ethyl, n-butyl, vinyl, allyl, 1-propenyl and 1-propynyl, or a group, which is optionally substituted with one or more halogen atom(s), methyl or methoxy group(s), selected from cyclopentyl, cyclohexyl, phenyl, benzyl, phenethyl, 2-thienyl and 3-furyl.

9. A compound according to claim 8, wherein R_4 represents a linear group selected from ethyl, n-butyl, vinyl, allyl and 1-propynyl, or a group, which is optionally substituted with one or more halogen atom(s), methyl or methoxy group(s), selected from cyclopentyl, phenyl, benzyl, phenethyl and 2-thienyl.

10. A compound according to any one of claims 8 and 9, wherein R_4 represents a group selected from ethyl, n-butyl, vinyl, allyl, cyclopentyl, phenyl, benzyl or 2-thienyl

11. A compound according to any one of claims 1 to 4, wherein R_2 is a group of formula ii), wherein Q represents a single bond or an oxygen atom.

12. A compound according to any one of the preceding claims wherein R_5 is hydrogen or hydroxy.

13. A compound according to any one of the preceding claims wherein p is 2 and the amide group is at positions 3 or 4 of the azabicyclic ring.

14. A compound according to claim 13 wherein the amide group is at position 3 of the azabicyclic ring.

15. A compound of formula (II) according to any one of claims 2 to 14, wherein m is an integer from 0 to 6 and n is an integer from 0 to 4; A represents a group selected from $-CH_2-$, -CH=CH-, –O-, -C(O)-, -NR'-, and -S-; and R_6 is a hydrogen atom, a cyano group, a nitro group, a -C(O)OR' group, a -OC(O)R' group, a -SC(O)R', group, a $-CH=CH_2$ group, a –CH=CR'R" group, a C(O)NR'R" group, a straight or branched C_1-C_4 alkyl group, which

is optionally substituted with one or more halogen atom(s), a straight C_1-C_4 alkoxy group, which is optionally substituted with one or more halogen atom(s) or hydroxy group(s), or a cyclic group, which is optionally substituted with one or more substituents selected from halogen atoms, groups of formula –C(O)NR'R" and methyl, hydroxy, nitro and phenyl groups, the cyclic group being selected from cyclohexyl, phenyl, 5,6,7,8-tetrahydronaphthanelyl, 2-thienyl, 1-pyrrolidinyl, 1-pyrrolyl, benzo[1,3]dioxolyl, 2-benzothiazolyl, naphthalenyl and dioxolyl.

16. A compound according to claim 15, wherein m is an integer from 0 to 5 and n is an integer from 0 to 2; A represents a group selected from $-CH_2-$, -CH=CH-, –O-, -C(O)-, -NR'-, and -S-; and R_6 is a hydrogen atom, a cyano group, a -C(O)OR' group, a -OC(O)R' group, a -SC(O)R', group, a $-CH=CH_2$ group, a -C(O)NR'R" group, a straight or branched C_1-C_4 alkyl group, a trifluoromethyl, or a cyclic group selected from cyclohexyl, ,5,6,7,8-tetrahydronaphthanelyl, 2-thienyl, 1-pyrrolyl, benzo[1,3]dioxolyl, 2-benzothiazolyl, naphthalenyl, dioxolyl and phenyl, which is optionally substituted with one or more substituents selected from halogen atoms, groups of formula –C(O)NR'R", methyl, hydroxy and phenyl groups.

17. A compound according to any one of claims 15 and 16, wherein m is an integer from 0 to 5 and n is an integer form 0 to 2; A represents a group selected from $-CH_2-$, -CH=CH-, –O-; and R_6 is selected from hydrogen, straight C_1-C_4 alkyl, $-CH=CH_2$, cyclohexyl, phenyl which is unsubstituted or substituted with one or two substituents selected from methyl groups and hydroxy groups, 5,6,7,8-tetrahydronaphthanelyl and 2-thienyl.

18. A compound according to claim 17, wherein the sequence R_6 - $(CH_2)_n$ – A – $(CH_2)_m$ – is one of methyl, 3-phenoxypropyl, 3-(3-hydroxyphenoxy)propyl, allyl, heptyl, 3-phenylpropyl, 3-phenylallyl, 2-phenoxyethyl, 2-benzyloxyethyl, cyclohexylmethyl, 3-(5,6,7,8-tetrahydronaphthalen-2-yloxy)propyl, 5-(2,6-dimethylphenoxy)pentyl, 3-thien-2-ylpropyl or 3-cyclohexylpropyl and X^- is bromide or trifluoroacetate.

19. A compound according to any one of the preceding claims, which is a single isomer.

20. A compound according to claim 1 or claim 2 which is one of:
N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-hydroxy-2,2-dithien-2-ylacetamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2,2-dithien-2-ylacetamide

N-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2,2-dithien-2-ylacetamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2,2-dithien-2-ylacetamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-cyclopentyl-2-hydroxy-2-thien-2-ylacetamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2-thien-2-ylpent-4-enamide
(2*)-N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2-thien-2-ylbutanamide (diastereomer 1)
(2*)-N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2-thien-2-ylbutanamide (diastereomer 2)
(2*)-N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2-thien-2-ylbut-3-enamide (diastereomer 1)
(2*)-N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-hydroxy-2-thien-2-ylbut-3-enamide (diastereomer 2)
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3-diphenylpropanamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-phenylhexanamide
N-(1-Azabicyclo[2.2.2]oct-3-yl)-9H-xanthene-9-carboxamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-9H-xanthene-9-carboxamide
N-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-9H-xanthene-9-carboxamide
N-(1-Azabicyclo[2.2.2]oct-3-yl)-9-hydroxy-9H-fluorene-9-carboxamide
N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-N-methyl-9H-xanthene-9-carboxamide
(2S)-N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-2-cyclopentyl-2-hydroxy-2-thien-2-ylacetamide
3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-methyl-1-azoniabicyclo[2.2.2]octane bromide
3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-methyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-1-Allyl-3-(2-hydroxy-2,2-dithien-2-ylacetylamino)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-1-Heptyl-3-(2-hydroxy-2,2-dithien-2-ylacetylamino)-1-azoniabicyclo[2.2.2]octane trifluoroacetate
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-((E)-3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-(2-Benzyloxyethyl)-3-(2-hydroxy-2,2-dithien-2-ylacetylamino)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-(3-thien-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3S)-3-(2-Hydroxy-2,2-dithien-2-ylacetylamino)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-(2,2-Dithien-2-ylacetylamino)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide

1-Methyl-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane bromide

1-(3-Phenoxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(3-Phenoxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane bromide

(3S)-1-Allyl-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3S)-1-Heptyl-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3S)-1-Cyclohexylmethyl-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3S)-1-(3-Cyclohexylpropyl)-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3S)-1-(3-Phenoxypropyl)-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane bromide

(3S)-1-[3-(5,6,7,8-Tetrahydronaphthalen-2-yloxy)propyl]-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3S)-1-[5-(2,6-Dimethylphenoxy)pentyl]-3-[(9H-xanthen-9-ylcarbonyl)amino]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

3-{[(9-Hydroxy-9H-fluoren-9-yl)carbonyl]amino}-1-methyl-1-azoniabicyclo[2.2.2]octane bromide

3-{[(9-Hydroxy-9H-fluoren-9-yl)carbonyl]amino}-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-[3-(2-Carbamoylphenoxy)propyl]-3-{[(9-Hydroxy-9H-fluoren-9-yl)carbonyl]amino}-1-azoniabicyclo[2.2.2]octane formate

(3R)-1-[4-(4-Fluorophenyl)-4-oxobutyl]-3-{[(9-Hydroxy-9H-fluoren-9-yl)carbonyl]amino}-1-azoniabicyclo[2.2.2]octane formate

(3R)-3-{[(9-Hydroxy-9H-fluoren-9-yl)carbonyl]amino}-1-[3-(methylphenylamino)propyl]-1-azoniabicyclo[2.2.2]octane chloride

(3R)-3-{[(9-Hydroxy-9H-fluoren-9-yl)carbonyl]amino}-1-(3-phenylsulfanylpropyl)-1-azoniabicyclo[2.2.2]octane formate

(3R)-3-[Methyl-(9H-xanthen-9-ylcarbonyl)amino]-1-(3-pyrrol-1-ylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-[3-(Biphenyl-4-yloxy)propyl]-3-[methyl-(9H-xanthene-9-carbonyl)amino]-1-azoniabicyclo[2.2.2]octane chloride

(3R)-3-(2-Fur-2-yl-2-hydroxypent-3-ynoylamino)-1-[3-(naphthalen-1-yloxy)propyl]-1-azoniabicyclo[2.2.2]octane chloride

(3R)-1-[3-(Benzo[1,3]dioxol-5-yloxy)propyl]-3-(2-fur-2-yl-2-hydroxypent-3-ynoylamino)-1-azonia-bicyclo[2.2.2]octane bromide

(3R)-1-[3-(Benzothiazol-2-yloxy)propyl]-3-(2-fur-2-yl-2-hydroxypent-3-ynoylamino)-1-azonia-bicyclo[2.2.2]octane chloride

(3R)-3-{[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetyl]amino}-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-{[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetyl]amino}-1-(2-ethoxyethyl)-1-azoniabicyclo[2.2.2]octane formate

(3R)-3-{[(2S)-2-Cyclopentyl-2-hydroxy-2-thien-2-ylacetyl]amino}-1-(4,4,4-trifluorobutyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(4-Acetoxybutyl)-3-[2-(5-bromothien-2-yl)-2-(4-fluoro-3-methylphenyl)-2-hydroxyacetylamino]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[2-(5-Bromothien-2-yl)-2-(4-fluoro-3-methylphenyl)-2-hydroxyacetylamino]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane bromide

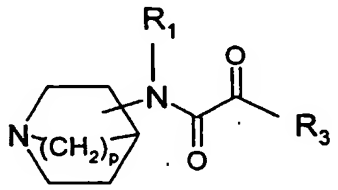
(3R)-1-(3-Acetylsulfanylpropyl)-3-[2-(5-bromothien-2-yl)-2-(4-fluoro-3-methylphenyl)-2-hydroxyacetylamino]-1-azoniabicyclo[2.2.2]octane formate

(3R)-1-(3-Cyanopropyl)-3-[2-fur-2-yl-2-hydroxy-4-(4-methoxyphenyl)butyrylamino]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(2-Carbamoylethyl)-3-[2-fur-2-yl-2-hydroxy-4-(4-methoxyphenyl)butyrylamino]-1-azoniabicyclo[2.2.2]octane formate

(3R)-1-(2-[1,3]Dioxolan-2-yl-ethyl)-3-[2-fur-2-yl-2-hydroxy-4-(4-methoxyphenyl)butyrylamino]-1-azoniabicyclo[2.2.2]octane bromide

21. A process for producing a compound of formula (I), as defined in claim 1 and wherein R_2 is a group of formula i) and R_5 is an hydroxy group, which process comprises reacting a compound of formula (V).



(V)

wherein R_1 and R_3 are as defined in claim 1 with the corresponding organometallic derivative R_4-[Mg,Li], wherein R_4 is as defined in claim 1.

22. A compound of formula (V), which is one of

N-1-azabicyclo[2.2.2]oct-3-yl-2-oxo-2-thien-2-ylacetamide

N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-2-oxo-2-thien-2-ylacetamide

N-[(3S)-1-Azabicyclo[2.2.2]oct-3-yl]-2-oxo-2-thien-2-ylacetamide

23. A process for producing a compound of formula (II), as defined in claim 2, which process comprises reacting a compound of formula (I), as defined in claim 1 with an alkylating agent of formula R_6-$(CH_2)_n$-A-$(CH_2)_m$-W, wherein R_6, n, A and m are as defined in claim 2 and W represents any suitable leaving group.

24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 20 in admixture with a pharmaceutically acceptable carrier or diluent.

25. A compound according to any one of claims1 to 20 for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

26. Use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

27. Use according to claim 26 wherein the pathological condition is a respiratory, urological or gastrointestinal disease or disorder.

28. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors, which comprises administering to said subject an effective amount of a compound as defined in any one of claims 1 to 20.

29. A method according to claim 28 wherein the pathological condition is a respiratory, urological or gastrointestinal disease or disorder.

30. A combination product comprising
(i) a compound according to any one of claims 1 to 20; and
(ii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder
for simultaneous, separate or sequential use.

31. A combination product according to claim 30 comprising
(i) a compound according to any one of claims 1 to 20; and
(ii) a β_2 agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonist for simultaneous, separate or sequential use in the treatment of a respiratory disease.